Science and Technology: Biology and Biotechnology

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I HAVE understood *science* to mean our effort to comprehend ourselves and the world we inhabit and to try to make or impose some sense on it. When Einstein winced at the thought that God might play dice, he was reflecting a deep unease about senselessness, not that he would be troubled about building a machine.

Technology is the use of scientific knowledge and insight to make things or practice processes that are inspired by someone's practical advantage.

Scientists cannot help stumbling onto technical innovations, and often justify investment in their work by the promise that innovations will follow. And technical praxis may be the means of corroborating the objective utility of a scientific generalization, carrying it beyond the domain of social construction of "the truth." On the other hand, praxis often uncovers limitations in scientific understanding and brings forth phenomena that provoke profound inquiry.

When a scientific principle is studied in the laboratory, it is subjected to controlled trials, the essence of which is to limit the number of incident variables. In technical or clinical application, or in natural history, nature—not human judgement—brings into play new variables, including some that had not previously been adjudged to be relevant. Thus, the discovery in 1944 that the genetic material was composed of DNA, took place at the Rockefeller Institute as the byproduct of studies on the classification of bacteria causing pneumonia.

From the very beginning, it was clear to the emerging practitioners of molecular biology—and I have been at it since 1944 or earlier—that there would eventually be enormous practical fallout from these axially important findings about the gene and the cell. In fact, as the years went by, I would lament that it took close to thirty-five years before it could be said that anyone's life had been saved by our knowledge of the structure of DNA. Until well into the 1960's, genetics was a marginal discipline in the teaching of medicine—having founded the departments at Wisconsin (1955) and Stanford (1959), I can testify to the struggle. Today, pharmaceutical, immunological, and pathological science and technology are dominated by the iconic vision of the double helix. We could not have begun to comprehend what the human immunodeficiency virus (HIV) was without that; nor could any of the now burgeoning drug treatments have been developed.

For now, I will rely on an article (Lederberg, 1993) that appeared originally in a series on molecular medicine in the *Journal of the American Medical Association* to spell out detailed examples. Besides medical application, DNA analysis has furnished the most spectacular advance in forensics, for criminal identification and the labeling of human remains, as well as the authentication of paternity. And biotechnology is beginning to make a dent in agriculture and in a few industrial chemical processes. For the latter there is much impetus from the avoidance of nonbiodegradable solvents, and from the positive use of biotechnology in environmental cleanup. But we are not yet past orchestrated fear of "genetically manipulated foods," especially in Europe, where it may of course serve as a nontariff barrier to trade.

The biotechnology industry had a market capitalization of $52 billion (on current sales of $9.3 billion, and research and development expenses of the same order) (Ernst and Young, 1996). Even today's skeptical market still has some optimism for future prospects. The picture is being blurred by the consolidation of many smaller biotechnology companies into the pharmaceutical giants, and by the belated incorporation of DNA-based strategies into their own research doctrine. Thirty-five years ago, I had zero takers when I tried to interest the pharmaceutical industry in a combinatorial (Darwinian) approach for drug discovery. Today, this is described as the central paradigm. My wise friends have told me that the resistance came from the establishment chemists who would be pained ever to let a compound out of their synthetic laboratories until they had purified and verified its structure. Anything else would be "Schmer chemistry," epitomized by Dr. Gottlieb's invective in *Arrowsmith.* It was bolstered by the expectation that theoretical structural analysis and x-ray determinations of drug-receptor fit would provide a rational basis for drug development. Only then could the pharmacologists and toxicologists be given access to it. My rejoinder had been that life could never have started on Earth if the Ur-Chemist had been similarly constrained.

Expectations of social utility and of profit are now plainly far more powerful motives for pursuing biological science than when I entered that vocation a half-century ago. Robert Merton's characterizations of scientific norms, may I call them the dignity of my profession, are a familiar portrait of what I remember. Scientists have always been jealous of their prestige, or priority in discovery; today many of them may have far more material pressures on their interpersonal and moral behavior. By its impact on technology, science may also matter more to the social body, with promises of medical advance and threats from earth-consuming pollution and weapons. The "rest of culture" does not notice, both in large (but perhaps now becoming asymptotic) governmental support for research, and in widely voiced anxieties about being overrun by technology that burgeons faster than anyone can understand its full implications.

Technology does, of course, guide the possibility of investigation in the modern laboratory, where string and sealing wax may be hard to find. Biology was one of the last of the natural sciences to eschew heavy-metal technology. I began my career, and as far as feasible still try, to practice science where the weight of ideas outbalances that of the equipment. (Not always: some of my experiments were carried out on Mars, thanks to rather large space rockets and a cast of thousands at the NASA command centers and engineering development programs. But those rockets would have been built and paid for regardless, and put to even more problematical applications, if exobiology had not been on the table.)

But coming back to earth, biology would be a poor competitor with physics in an Aristophanean competition weighing chariots against fleets of ships in the literary competition of Aeschylus versus Euripides.

Stacked up against the major accelerators, our moderate size machines are represented by six-digit, not ten-digit, investments: the electron microscope, x-ray diffraction, Nuclear Magnetic Resonance, and the robotocized gene-sequencers and -synthesizers; and the latter can be commercialized, retailed, and leased out for a few hundred dollars a shot. Most laboratories budget more for graduate and postdoctorate assistants than for equipment. In fact, some of the most rewarding technical developments have eventuated in becoming smaller and cheaper. The simple agar gel electro-powered diffusion (gel electrophoresis) has replaced expensive ultra-centrifuges. And the polymerase chain reaction (PCR) technology was named "molecule" of the year for having democratized access to DNA. The kits for PCR cost just a few hundred dollars and they offer the detectability of just single molecules of DNA and easy clues to the structure of the tiniest samples.

In fact, we have an agenda for productive biological research for the next century that requires no new ideas at all: to tease out the one hundred thousand or so genes that populate the entire human genome (which has room for ten million). This can clearly be done within the scale of research and development investment of the biotechnology industry, and some multiple to spare for the real task of teasing out the functions and the interactions of all these genes. Just within the last year we have seen the mapping of several bacteria and of yeast; and the first order of maps of the human are in sight. Some firms have the expectation that by this mechanical sequencing of a gene, or tag ends of it, they may gain property rights to any further use of that knowledge—that still has to be fought out in the courts and in the Congress.

The mechanical production of all this new knowledge is quite wonderful; but how widely is it understood that it is just the first step? I have no doubt at all that some significant percentage, perhaps ten thousand genes, will prove to have important biomedical application. But history tells us that to bring any one to practice involves bare minimum investment of $100 million each. So we do have a triage problem of the scale of the GNP; that is, measured in trillions of dollars. The effort, even when trimmed, might exhaust all of our intellectual as well as financial resources; and in that setting will we again have fresh breakthroughs like those of 1944? The opening up of fresh paradigms, beyond what can be programmed from Washington, or even by a hidden hand that is stuffed with lucre?

References

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